

NDA 19-651/S-010
NDA 19-651/S-011

AUG 14 2000

Procter & Gamble Pharmaceuticals
Attention: Lenore Faulhaber, Ph.D., M.B.A.
US Regulatory Affairs Manager
Health Care Research Center
8700 Mason-Montgomery Road
Mason, OH 45040-9462

Dear Dr. Faulhaber:

Please refer to your supplemental new drug applications dated August 19 and September 5, 1999, received August 20 and October 7, 1999, respectively, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Asacol (mesalamine) Tablets.

We acknowledge receipt of your submissions dated April 7 and June 20, 2000. Your submission of June 20, 2000 constituted a complete response to our February 16, 2000 action letter.

These "Changes Being Effected" supplemental new drug applications provide for the following

Supplement —010 provides for revision of the package insert to include a Geriatric Use subsection in the PRECAUTIONS section, along with language about potential renal toxicity, in accordance with 21 CFR 201 .57(f)(10)(ii)(A) and 201 .57(f)(10)(iii)(B), respectively.

Supplement —011 provides for revision of the ADVERSE REACTIONS section of the package insert to include 1) language about hepatotoxicity in patients exposed to mesalamine and 2) two new adverse events: lupus-like syndrome and pleuritis.

We have completed the review of these supplemental applications, as amended, and have concluded that adequate information has been presented to demonstrate that the drug products are safe and effective for use as recommended in the submitted final printed labeling (package insert submitted June 20, 2000). Accordingly, these supplemental applications are approved effective on the date of this letter.

Please eliminate duplication of the word "malaise" in the second paragraph of the ADVERSE REACTIONS section. This revision can be made at the next printing of the package insert, and the Division notified in the subsequent annual report.

If a letter communicating important information about this drug product (i.e., a "Dear Health Care Practitioner" letter) is issued to physicians and others responsible for patient care, we -

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request that you submit a copy of the letter to this NDA and a copy to the following address:

MED WATCH, HF-2
FDA
5600 Fishers Lane
Rockville, MD 20857

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

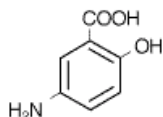
If you have any questions, call Melodi McNeil, Regulatory Health Project Manager, at (301) 827-7310.

Sincerely,

Lilia Talarico, M.D.
Director
Division of Gastrointestinal and Coagulation Drug
Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Asacol[®] (mesalamine) Delayed-Release Tablets

DESCRIPTION: Each **Asacol** delayed-release tablet for oral administration contains 400 mg of mesalamine, an anti-inflammatory drug. The **Asacol** delayed-release tablets are coated with acrylic based resin, Eudragit S (methacrylic acid copolymer B, NF), which dissolves at pH 7 or greater, releasing mesalamine in the terminal ileum and beyond for topical anti-inflammatory action in the colon. Mesalamine has the chemical name 5-amino-2-hydroxybenzoic acid; its structural formula is:



Molecular Weight: 153.1
Molecular Formula: C₇H₇NO₃

Inactive Ingredients: Each tablet contains colloidal silicon dioxide, dibutyl phthalate, edible black ink, iron oxide red, iron oxide yellow, lactose, magnesium stearate, methacrylic acid copolymer B (Eudragit S), polyethylene glycol, povidone, sodium starch glycolate, and talc.

CLINICAL PHARMACOLOGY: Mesalamine is thought to be the major therapeutically active part of the sulfasalazine molecule in the treatment of ulcerative colitis. Sulfasalazine is converted to equimolar amounts of sulfapyridine and mesalamine by bacterial action in the colon. The usual oral dose of sulfasalazine for active ulcerative colitis is 3 to 4 grams daily in divided doses, which provides 1.2 to 1.6 grams of mesalamine to the colon.

The mechanism of action of mesalamine (and sulfasalazine) is unknown, but appears to be topical rather than systemic. Mucosal production of arachidonic acid (AA) metabolites, both through the cyclooxygenase pathways, i.e., prostanoids, and through the lipoxygenase pathways, i.e., leukotrienes (LTs) and hydroxyeicosatetraenoic acids (HETEs), is increased in patients with chronic inflammatory bowel disease, and it is possible that mesalamine diminishes inflammation by blocking cyclooxygenase and inhibiting prostaglandin (PG) production in the colon.

Pharmacokinetics: **Asacol** tablets are coated with an acrylic-based resin that delays release of mesalamine until it reaches the terminal ileum and beyond. This has been demonstrated in human studies conducted with radiological and serum markers. Approximately 28% of the mesalamine in **Asacol** tablets is absorbed after oral ingestion, leaving the remainder available for topical action and excretion in the feces. Absorption of mesalamine is similar in fasted and fed subjects. The absorbed mesalamine is rapidly acetylated in the gut mucosal wall and by the liver. It is excreted mainly by the kidney as N-acetyl-5-aminosalicylic acid.

Mesalamine from orally administered **Asacol** tablets appears to be more extensively absorbed than the mesalamine released from sulfasalazine. Maximum plasma levels of mesalamine and N-acetyl-5-aminosalicylic acid following multiple **Asacol** doses are

about 1.5 to 2 times higher than those following an equivalent dose of mesalamine in the form of sulfasalazine. Combined mesalamine and N-acetyl-5-aminosalicylic acid AUC's and urine drug dose recoveries following multiple doses of **Asacol** tablets are about 1.3 to 1.5 times higher than those following an equivalent dose of mesalamine in the form of sulfasalazine.

The t_{max} for mesalamine and its metabolite, N-acetyl-5-aminosalicylic acid, is usually delayed, reflecting the delayed release, and ranges from 4 to 12 hours. The half-lives of elimination (t_{1/2elm}) for mesalamine and N-acetyl-5-aminosalicylic acid are usually about 12 hours, but are variable, ranging from 2 to 15 hours. There is a large intersubject variability in the plasma concentrations of mesalamine and N-acetyl-5-aminosalicylic acid and in their elimination half-lives following administration of **Asacol** tablets.

Clinical Studies: Mildly to moderately active ulcerative colitis: Two placebo-controlled studies have demonstrated the efficacy of **Asacol** tablets in patients with mildly to moderately active ulcerative colitis. In one randomized, double-blind, multi-center trial of 158 patients, **Asacol** doses of 1.6 g/day and 2.4 g/day were compared to placebo. At the dose of 2.4 g/day, **Asacol** tablets reduced the disease activity, with 21 of 43 (49%) **Asacol** patients showing improvement in sigmoidoscopic appearance of the bowel compared to 12 of 44 (27%) placebo patients ($p = 0.048$). In addition, significantly more patients in the **Asacol** 2.4 g/day group showed improvement in rectal bleeding and stool frequency.

The 1.6 g/day dose did not produce consistent evidence of effectiveness.

In a second randomized, double-blind, placebo-controlled clinical trial of 6 weeks duration in 87 ulcerative colitis patients, **Asacol** tablets, at a dose of 4.8 g/day, gave sigmoidoscopic improvement in 28 of 38 (74%) patients compared to 10 of 38 (26%) placebo patients ($p < 0.001$). Also, more patients in the **Asacol** 4.8 g/day group showed improvement in overall symptoms.

Maintenance of remission of ulcerative colitis: A 6-month, randomized, double-blind, placebo-controlled, multi-center study involved 264 patients treated with **Asacol** 0.8 g/day ($n = 90$), 1.6 g/day ($n = 87$), or placebo ($n = 87$). The proportion of patients treated with 0.8 g/day who maintained endoscopic remission was not statistically significant compared to placebo. In the intention to treat (ITT) analysis of all 174 patients treated with **Asacol** 1.6 g/day or placebo, **Asacol** maintained endoscopic remission of ulcerative colitis in 61 of 87 (70.1%) of patients, compared to 42 of 87 (48.3%) of placebo recipients ($p = 0.005$).

A pooled efficacy analysis of 4 maintenance trials compared **Asacol**, at doses of 0.8 g/day to 2.8 g/day, with sulfasalazine, at doses of 2 g/day to 4 g/day ($n = 200$). Treatment success was 59 of 98 (59%) for **Asacol** and 70 of 102 (69%) for sulfasalazine, a non-significant difference.

Study to assess the effect on male fertility: The effect of **Asacol** (mesalamine) on sulfasalazine-induced impairment of male fertility was examined in an open-label study.

Nine patients (age < 40 years) with chronic ulcerative colitis in clinical remission on sulfasalazine 2 g/day to 3 g/day were crossed over to an equivalent **Asacol** dose (0.8 g/day to 1.2 g/day) for 3 months. Improvement in sperm count ($p < 0.02$) and morphology ($p < 0.02$) occurred in all cases. Improvement in sperm motility ($p < 0.001$) occurred in 8 of the 9 patients.

INDICATIONS AND USAGE: **Asacol** tablets are indicated for the treatment of mildly to moderately active ulcerative colitis and for the maintenance of remission of ulcerative colitis.

CONTRAINDICATIONS: **Asacol** tablets are contraindicated in patients with hypersensitivity to salicylates or to any of the components of the **Asacol** tablet.

PRECAUTIONS: General: Patients with pyloric stenosis may have prolonged gastric retention of **Asacol** tablets which could delay release of mesalamine in the colon.

Exacerbation of the symptoms of colitis has been reported in 3% of **Asacol**-treated patients in controlled clinical trials. This acute reaction, characterized by cramping, abdominal pain, bloody diarrhea, and occasionally by fever, headache, malaise, pruritus, rash, and conjunctivitis, has been reported after the initiation of **Asacol** tablets as well as other mesalamine products. Symptoms usually abate when **Asacol** tablets are discontinued.

Some patients who have experienced a hypersensitivity reaction to sulfasalazine may have a similar reaction to **Asacol** tablets or to other compounds which contain or are converted to mesalamine.

Renal: Renal impairment, including minimal change nephropathy, and acute and chronic interstitial nephritis, has been reported in patients taking **Asacol** tablets as well as other compounds which contain or are converted to mesalamine. In animal studies (rats, dogs), the kidney is the principal target organ for toxicity. At doses of approximately 750 mg/kg to 1000 mg/kg [15 to 20 times the administered recommended human dose (based on a 50 kg person) on a mg/kg basis and 3 to 4 times on a mg/m² basis], mesalamine causes renal papillary necrosis. **Therefore, caution should be exercised when using Asacol (or other compounds which contain or are converted to mesalamine or its metabolites) in patients with known renal dysfunction or history of renal disease. It is recommended that all patients have an evaluation of renal function prior to initiation of Asacol tablets and periodically while on Asacol therapy.**

Information for Patients: Patients should be instructed to swallow the **Asacol** tablets whole, taking care not to break the outer coating. The outer coating is designed to remain intact to protect the active ingredient and thus ensure mesalamine availability for action in the colon. In 2% to 3% of patients in clinical studies, intact or partially intact tablets have been reported in the stool. If this occurs repeatedly, patients should contact their physician.

Patients with ulcerative colitis should be made aware that ulcerative colitis rarely remits completely, and that the risk of relapse can be substantially reduced by continued administration of **Asacol** at a maintenance dosage.

Drug Interactions: There are no known drug interactions.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Dietary mesalamine was not carcinogenic in rats at doses as high as 480 mg/kg/day, or in mice at 2000 mg/kg/day. These doses are 2.4 and 5.1 times the maximum recommended human maintenance dose of **Asacol** of 1.6 g/day (32 mg/kg/day if 50 kg body weight assumed or 1184 mg/m²), respectively, based on body surface area. Mesalamine was negative in the Ames assay for mutagenesis, negative for induction of sister chromatid exchanges (SCE) and chromosomal aberrations in Chinese hamster ovary cells *in vitro*, and negative for induction of micronuclei (MN) in mouse bone marrow polychromatic erythrocytes. Mesalamine, at oral doses up to 480 mg/kg/day, had no adverse effect on fertility or reproductive performance of male and female rats.

Pregnancy: Teratogenic Effects: Pregnancy Category B: Reproduction studies in rats and rabbits at oral doses up to 480 mg/kg/day have revealed no evidence of teratogenic effects or fetal toxicity due to mesalamine. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Nursing Mothers: Low concentrations of mesalamine and higher concentrations of its N-acetyl metabolite have been detected in human breast milk. While the clinical significance of this has not been determined, caution should be exercised when mesalamine is administered to a nursing woman.

Pediatric Use: Safety and effectiveness of **Asacol** tablets in pediatric patients have not been established.

Geriatric Use: Clinical studies of **Asacol** did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy in elderly patients should be considered when prescribing **Asacol**.

This drug is known to be substantially excreted by the kidney, and the risk of toxic reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken when prescribing this drug therapy. As stated in the PRECAUTIONS section, it is recommended that all patients have an evaluation of renal function prior to initiation of **Asacol** tablets and periodically while on **Asacol** therapy.

ADVERSE REACTIONS: **Asacol** tablets have been evaluated in 3685 inflammatory bowel disease patients (most patients with ulcerative colitis) in controlled and open-label studies. Adverse events seen in clinical trials with **Asacol** tablets have generally been mild and reversible. Adverse events presented in the following sections may occur regardless of length of therapy and similar events have been reported in short- and long-term studies and in the post-marketing setting.

In two short-term (6 weeks) placebo-controlled clinical studies involving 245 patients, 155 of whom were randomized to **Asacol** tablets, five (3.2%) of the **Asacol** patients

discontinued **Asacol** therapy because of adverse events as compared to two (2.2%) of the placebo patients. Adverse reactions leading to withdrawal from **Asacol** tablets included (each in one patient): diarrhea and colitis flare; dizziness, nausea, joint pain, and headache; rash, lethargy and constipation; dry mouth, malaise, lower back discomfort, mild disorientation, mild indigestion and cramping; headache, nausea, malaise, aching, vomiting, muscle cramps, a stuffy head, plugged ears, and fever.

Adverse events occurring in **Asacol**-treated patients at a frequency of 2% or greater in the two short-term, double-blind, placebo-controlled trials mentioned above are listed in Table 1 below. Overall, the incidence of adverse events seen with **Asacol** tablets was similar to placebo.

Table 1

Frequency (%) of Common Adverse Events Reported in Ulcerative Colitis Patients Treated with **Asacol** Tablets or Placebo in Short-Term (6-Week) Double-Blind Controlled Studies

<u>Event</u>	<u>Percent of Patients with Adverse Events</u>	
	<u>Placebo (n = 87)</u>	<u>Asacol tablets (n = 152)</u>
Headache	36	35
Abdominal pain	14	18
Eructation	15	16
Pain	8	14
Nausea	15	13
Pharyngitis	9	11
Dizziness	8	8
Asthenia	15	7
Diarrhea	9	7
Back pain	5	7
Fever	8	6
Rash	3	6
Dyspepsia	1	6
Rhinitis	5	5
Arthralgia	3	5
Hypertonia	3	5
Vomiting	2	5
Constipation	1	5
Flatulence	7	3
Dysmenorrhea	3	3
Chest pain	2	3
Chills	2	3

Flu syndrome	2	3
Peripheral edema	2	3
Myalgia	1	3
Sweating	1	3
Colitis exacerbation	0	3
Pruritus	0	3
Acne	1	2
Increased cough	1	2
Malaise	1	2
Arthritis	0	2
Conjunctivitis	0	2
Insomnia	0	2

Of these adverse events, only rash showed a consistently higher frequency with increasing **Asacol** dose in these studies.

In a 6-month placebo-controlled maintenance trial involving 264 patients, 177 of whom were randomized to **Asacol** tablets, six (3.4%) of the **Asacol** patients discontinued **Asacol** therapy because of adverse events, as compared to four (4.6%) of the placebo patients. Adverse reactions leading to withdrawal from **Asacol** tablets included (each in one patient): anxiety; headache; pruritus; decreased libido; rheumatoid arthritis; and stomatitis and asthenia.

In the 6-month placebo-controlled maintenance trial, the incidence of adverse events seen with **Asacol** tablets was similar to that seen with placebo. In addition to events listed in Table 1, the following adverse events occurred in **Asacol**-treated patients at a frequency of 2% or greater in this study: abdominal enlargement, anxiety, bronchitis, ear disorder, ear pain, gastroenteritis, gastrointestinal hemorrhage, infection, joint disorder, migraine, nervousness, paresthesia, rectal disorder, rectal hemorrhage, sinusitis, stool abnormalities, tenesmus, urinary frequency, vasodilation, and vision abnormalities.

In 3342 patients in uncontrolled clinical studies, the following adverse events occurred at a frequency of 5% or greater and appeared to increase in frequency with increasing dose: asthenia, fever, flu syndrome, pain, abdominal pain, back pain, flatulence, gastrointestinal bleeding, arthralgia, and rhinitis.

In addition to the adverse events listed above, the following events have been reported in clinical studies, literature reports, and postmarketing use of products which contain (or have been metabolized to) mesalamine. Because many of these events were reported voluntarily from a population of unknown size, estimates of frequency cannot be made. These events have been chosen for inclusion due to their seriousness or potential causal connection to mesalamine:

Body as a Whole: Neck pain, facial edema, edema, lupus-like syndrome.

Cardiovascular: Pericarditis (rare), myocarditis (rare).

Gastrointestinal: Anorexia, pancreatitis, gastritis, increased appetite, cholecystitis, dry mouth, oral ulcers, perforated peptic ulcer (rare), bloody diarrhea. There have been rare reports of hepatotoxicity including, jaundice, cholestatic jaundice, hepatitis, and possible hepatocellular damage including liver necrosis and liver failure. Some of these cases were fatal. Asymptomatic elevations of liver enzymes which usually resolve during continued use or with discontinuation of the drug have also been reported. One case of Kawasaki-like syndrome which included changes in liver enzymes was also reported.

Hematologic: Agranulocytosis (rare), aplastic anemia (rare), thrombocytopenia, eosinophilia, leukopenia, anemia, lymphadenopathy.

Musculoskeletal: Gout.

Nervous: Depression, somnolence, emotional lability, hyperesthesia, vertigo, confusion, tremor, peripheral neuropathy (rare), transverse myelitis (rare), Guillain-Barré syndrome (rare).

Respiratory/Pulmonary: Eosinophilic pneumonia, interstitial pneumonitis, asthma exacerbation, pleuritis.

Skin: Alopecia, psoriasis (rare), pyoderma gangrenosum (rare), dry skin, erythema nodosum, urticaria.

Special Senses: Eye pain, taste perversion, blurred vision, tinnitus.

Urogenital: Interstitial nephritis (See also Renal subsection in PRECAUTIONS), minimal change nephropathy (See also Renal subsection in PRECAUTIONS), dysuria, urinary urgency, hematuria, epididymitis, menorrhagia.

Laboratory Abnormalities: Elevated AST (SGOT) or ALT (SGPT), elevated alkaline phosphatase, elevated GGT, elevated LDH, elevated bilirubin, elevated serum creatinine and BUN.

DRUG ABUSE AND DEPENDENCY:

Abuse: None reported.

Dependency: Drug dependence has not been reported with chronic administration of mesalamine.

OVERDOSAGE: Two cases of pediatric overdose have been reported. A 3-year-old male who ingested 2 grams of **Asacol** tablets was treated with ipecac and activated charcoal; no adverse events occurred. Another 3-year-old male, approximately 16 kg, ingested an unknown amount of a maximum of 24 grams of **Asacol** crushed in solution (i.e., uncoated mesalamine); he was treated with orange juice and activated charcoal, and experienced no adverse events. In dogs, single doses of 6 grams of delayed-release **Asacol** tablets resulted in renal papillary necrosis but were not fatal. This was approximately 12.5 times the recommended human dose (based on a dose of 2.4 g/day in a 50 kg person). Single oral doses of uncoated mesalamine in mice and rats of 5000 mg/kg and 4595 mg/kg, respectively, or of 3000 mg/kg in cynomolgus monkeys, caused significant lethality.

DOSAGE AND ADMINISTRATION: For the treatment of mildly to moderately active ulcerative colitis: The usual dosage in adults is two 400-mg tablets to be taken three

times a day for a total daily dose of 2.4 grams for a duration of 6 weeks.

For the maintenance of remission of ulcerative colitis: The recommended dosage in adults is 1.6 grams daily, in divided doses. Treatment duration in the prospective, well-controlled trial was 6 months.

HOW SUPPLIED: Asacol tablets are available as red-brown, capsule-shaped tablets containing 400 mg mesalamine and imprinted "Asacol NE" in black.

NDC 0149-0752-02 Bottle of 100

Store at controlled room temperature 20°- 25°C (68°- 77°F) [See USP].

Procter & Gamble Pharmaceuticals Cincinnati, Ohio 45202 under license from Tillotts Pharma AG, the registered trademark owner, and Medeva PLC Made in Germany, D-64331 Weiterstadt U.S. Patent Nos. 5,541,170 and 5,541,171

REVISED APRIL 2000